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DATE MAILED: 06/27/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/970,045	Kovenetal
Examiner	**Group Art Unit**
Duffy	1645

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 2-1-99 & 8-26-99.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disp sition of Claims

☒ Claim(s) 1-13 & 39-47 is/are pending in the application.

Of the above claim(s)_____ is/are withdrawn from consideration.

☐ Claim(s)_____ is/are allowed.

☒ Claim(s) 1-13 & 39-47 is/are rejected.

☐ Claim(s)_____ is/are objected to.

☐ Claim(s)_____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on_____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on_____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)_____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received:_____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 6, mailed 2/1/99 ☐ Interview Summary, PTO-413

☒ Notice of Reference(s) Cited, PTO-892 ☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948 ☐ Other_____

Office Acti n Summary

Response to Amendment

1. The amendments filed 2-1-99 and 8-26-99 have been entered into the record. Claims 30-33 are canceled. Claims 1-13 and 39-47 are pending and under examination.

2. The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Rejections Withdrawn

3. Claims 4 and 5 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is withdrawn based on applicants declaration.

New Rejections Based on Amendment

Claim Rejections - 35 USC § 112

4. Claim 39 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 39 is drawn to the use of antibodies which bind HDL or LDL but do not cross react with LDL or HDL respectively. These antibodies do not apparently have written description support in the specification as originally filed. Applicants should point to the specification by

specific page and line number were cross reactivity issues of specific monoclonal antibodies are delineated.

5. Claims 1-12, 40, 41, 43, 45 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claim 1 and every claim dependent thereon (2-11), the claims are confusing since it is unclear that each of the first and second antibodies must bind different lipoproteins or apolipoproteins in order to affect a ratio. In the absence of such a recitation, the claims lack key elements which are required for an assay to result in the determination of a ratio of different lipoproteins or apolipoproteins. It is unclear as to which first of second antibody binds which apolipoprotein. The lack of clear antecedent basis in these claims renders it unclear as to what binds what and how the ratio is affected with respect to apolipoproteins. The claim are also confusion because the "at least a first and second monoclonal antibody molecules immunoreactive with a specific lipoprotein indicative of LDL or HDL...". As previously set forth, standard terminology in this field of art indicates that lipoprotein are particles comprised of multiple individual apolipoproteins. This concept is clearly enunciated by applicants in pages 1-2 of the specification. Thus, it is unclear what applicants intend by the recitation of "at least a first and second monoclonal antibody molecules immunoreactive with a specific lipoprotein indicative of LDL or HDL..." Do applicants intend to indicate ---a specific apolipoprotein indicative of LDL or HDL--?.

As to claim 2, the claim is confusing since many of the terms lack antecedent basis in claim 1 and provide for a combination with VLDL which lacks antecedent basis in claim 1.

As to claims 3-5, the claim recites "the antibody" but the independent claim recites at least two antibodies, which one is applicant referring to ?

As to claim 6, the recitation of "lipid associating with apolipoprotein" lacks antecedent basis in claim 1 and does not further limit this claim. Claim 1 is determining the amount of LDL and HDL or at least two different apolipoproteins. The determination of lipid does not determining the amount of LDL and HDL or at least two different apolipoproteins and does not provide for a ratio as indicated in the preamble and correlation of the claims.

As to claim 9, this claim is uninterpretable and unsearchable. It is unclear how this assay works to detect an apolipoprotein when a third antibody is coupled to a protein stain binds with an undefined apolipoprotein but it is unclear as to which one and moreover includes a stained second antibody bound apolipoprotein. The stained second antibody bound binds which apolipoprotein Applicants' should craft the claims such that a first and second apolipoprotein are clearly delineated and that the antibodies used in the assay clearly bind one apolipoprotein or the other, such that the antecedent basis in the claims is clear and unambiguous. Moreover, the claim depends from claim 6, which is drawn to detection using a lipid stain and "the stained second antibody-bound lipoprotein" lacks antecedent basis.

As to claim 12, it is unclear as to which first of second antibody binds which apolipoprotein, the claim indicates that there are at least two. The lack of clear antecedent basis in these claims renders it unclear as to what antibody binds what apolipoprotein and how the ratio is affected with respect to the two apolipoproteins. Additionally, it is unclear how the apolipoproteins are distinguished each from the other because the mixed sample contains at least two apolipoproteins which have two antibodies bound and a third antibody immobilized. How is separate quantitation achieved. How are two separate apolipoproteins detected ? The method steps are missing unknown undefined critical elements which is required to achieve quantitation of two separate apolipoproteins.

maintained.

As to claim 13, the claim is rendered confusing because the independent claim recites "at least two apolipoproteins, however claim 13 recites wherein "the apolipoprotein is" and it is unclear which one is referenced, the first or the second ?

6. As to claim 40, the claim in line 11, states "... separating the complexed antibody-lipoprotein particles from the biological sample.." is renders the claims unclear since it is unclear which complexes are separated and how. It appears that the lipoproteins complexed with the Apo CIII antibody separated and thus it is unclear how determining the amount of Apo C-III associated with Apo B is achieved when the pan B antibody is added to the biological sample and not the mixture of the sample and anti-Apo-C antibody. The claims do not make it clear how both antibodies make it into the same sample. The same concern is apparent for the recitation of "... contacting the anti-Apo A-I antibody with the biological sample" in the latter half of the assay for HDL.

As to claim 41, the claim, states "... separating the complexed antibody-lipoprotein particles from the biological sample.." is renders the claims unclear since it is unclear which complexes are separated and how. It appears that the lipoproteins complexed with the Apo E antibody separated and thus it is unclear how determining the amount of ApoE associated with Apo B is achieved when the pan B antibody is added to the biological sample and not the mixture of the sample and anti-Apo-E antibody. The claims do not make it clear how both antibodies make it into the same sample, nor do they clearly delineate that population which is being separated. The same concern is apparent for the later recitation in the second half of the assay for determining the amount of HDL. The term "predominantly" in the claim is a relative term which renders the claim indefinite. The term " monoclonal antibody which binds to Apo E predominantly associated with HDL [or VLDL]" in the claim is apparently a relative term of

binding degree which renders the claim indefinite. The term "predominately" is not defined by the claim, the specification does not provide what degree of binding would be encompassed by "predominantly" or provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

As to claims 43, 45 and 47, the claims are rendered indefinite since the recitation of "the monoclonal or recombinant antibody molecules specifically immunoreactive with a single specific lipoprotein or apolipoprotein are selected from the group consisting of ....." lacks antecedent basis in the claims from which they depend.

Claim Rejections - 35 USC § 102 and 103

7. Claims 46 and 47 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Curtiss et al (U.S. Patent 4,677,057, issued June 30, 1987).

Curtiss et al teach monoclonal antibodies specific for apolipoprotein AI (ApoAI) and apolipoprotein AII (Apo AII; see column 22, lines 34-67). Curtiss et al teach that the monoclonal antibody HA61 H112F3.1A11 (HB 8743) bound 100 percent of Apo AII on HDL and that all ApoII molecules expressed the epitope defined by this antibody (see column 27, fifth full paragraph to column 28, first full paragraph). This antibody meets the limitation of stable conformational epitope uninfluenced by other lipoproteins (i.e. specific binding). Curtiss et al teach diagnostic systems combining two or more such receptors (see column 22, seventh full paragraph). Thus, Curtiss et al anticipates the instantly claimed kits.

8. Claims 1, 2, 3, 10 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992) in view of Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988) in view of Forster et al (Biochem.

Soc. Trans. 18(6):1180, December 1990) and Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990).

The claims are drawn to measurement of a ratio of at least two apolipoproteins or a specific protein indicative of HDL or LDL by immersing into the sample a solid phase material having separately immobilized thereon at least first and second monoclonal antibody molecules immunoreactive with a specific lipoprotein indicative of LDL, HDL or at least two different apolipoproteins, removing the solid phase material, determining the amount of LDL, HDL or at least two different apolipoproteins and determining the ration of the LDL, HDL or at least two different lipoproteins.

Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992) teach a solid phase card based assay system which provides for analyzing a particular sample for different analytes (see column 2, lines 58-68; column 4, lines 50-55). The card provides a plurality of tabs. Each of the tabs has at least one receptor for the same analyte and may have a plurality of receptors for different analytes. The receptors are immobilized (see column 6, lines 55-62) on the tab(s) thereby allowing the simultaneous assay of a plurality of analytes in a single sample. The receptors are selectively attached a prearranged locations to the support, and where the analyte is an antigen the receptor would be a specific antibody (see column 7, lines 54-62). The card-like support can be dipped into the sample (see column 8, lines 24-34). A sufficient time is allowed for the interaction of the analyte and the receptor, the support is washed. The washed support is developed by a variety of means using a probe containing solution to quantitatively or qualitatively establish the presence of the analytes. The detection is provided by a variety of means including sandwich immunoassay , development of a color reaction, radioactive assay etc (see column 6, lines 1-15). Fish et al teach how to make the binding reaction quantitative (see

column 12, first and second full paragraphs). Fish et al teach that the card may be developed in the office under field conditions, or in the laboratory (see column 9, lines 15-16). Fish et al differs by not using monoclonal antibodies for apolipoproteins or specific lipoprotein indicative of HDL and LDL on the dipstick for immunoassay and not measuring a ratio thereof.

Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988) teaches methods for the determination of Apolipoprotein B-100 (Apo B-100) to apolipoprotein AI (Apo AI) using enzyme linked immunoassay sandwich techniques wherein the monoclonal antibodies specific for Apo B-100 (page 30, lines 30-41) and Apo AI (page 27-28) are immobilized on a solid phase, contacted with a sample, and the bound lipoproteins or apolipoprotein were detected. The detection was performed with an enzyme-linked monoclonal or polyclonal antibodies specific for Apo B-100 and Apo AI. Scripps Clinic and Research Foundation also teach that the immobilized antibody, sample and detection antibody simultaneously (see pages 33-34, claim 6).

Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990) teach the development of a simple dipstick measurement of apolipoproteins. Forster et al teach a sandwich assay for Apo AI or Apo B, wherein one of the antibodies is bound to the dipstick. The dipstick is immersed into the sample. After a certain amount of time the stick is removed and immersed in a developing reagent to detect Apo AI or Apo B. The presence of Apo AI or Apo B is detected using an enzyme-labeled second antibody or added to the sample a small amount of the corresponding enzyme-labeled apolipoprotein which acts as a tracer. Forster et al teach that Apo AI and Apo B are the major protein components of high-density lipoproteins (HDL) and low-density lipoproteins (LDL) respectively (i.e. the instant specific lipoprotein indicative of HDL and LDL). Forster et al teach that the dipstick test is being developed to test for an ApoB/AI ratio

which has the advantage of use in on the spot testing in general practitioners' surgeries or out-patient clinics.

Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) teach that the ratios of ApoA-I/ApoB are helpful in the diagnosis and differential diagnosis of coronary heart disease.

As to claims 1, and 2, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the multi-analyte card sandwich immunoassay of Fish et al by separately immobilizing the monoclonal antibodies specific for Apo B-100 (page 30, lines 30-41) and Apo AI (page 27-28) at prearranged places on the solid support tab in order to simultaneously perform the sandwich immunoassays of the Scripps Clinic and Research Foundation by employing the modified card tab assay to quantitate and determine lipoprotein or apolipoprotein ratios because Forster et al teach that apolipoproteins can be measured by a simple dipstick immunoassay and provide the advantage of use in on the spot testing in general practitioners' surgeries or out-patient clinics, that Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) teach that the ratios of ApoA-I/ApoB are helpful in the diagnosis and differential diagnosis of coronary heart disease, multi-analyte testing would save substantial time and reagents, and the substitution of one solid phase for another is quite routine in the art. As to claim 3, it would have also been *prima facie* obvious to one of ordinary skill in the art to use antigen binding fragments or recombinant antibodies of the monoclonal antibodies in the method as combined above because these antibodies would function equivalently in the assay as combined and such substitutions are routine in the art.

9. Claims 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992) in view of Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans.

18(6):1180, December 1990) and Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) as applied to claims 1, 2, 3, and 10 above, and further in view of Scripps Clinic (EP 0 257 778, published 2/3/88).

Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990) and Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) are set forth supra. The combination differs by not combining the labeled detection antibody with the sample prior to immersing the multi-analyte card into the sample.

Scripps Clinic (EP 0 257 778, published 2/3/88) teaches an indirect solid phase immunoassay for Apo B100 using two monoclonal antibodies wherein one monoclonal antibody is immobilized on a solid phase and the other labeled monoclonal antibody to a second epitope is added to the sample to form an immunoreaction mixture before contacting with the solid phase (page 13, see lines 38-42).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to mix the labeled detection antibodies for Apo AI and Apo B100 (i.e. probe) with the sample prior to the immersion of the multi-analyte solid phase card in the immunoassay as combined supra because Scripps Clinic teaches that (EP 0 257 778, published 2/3/88) the detection monoclonal antibody drawn to a second epitope on the apolipoprotein can be mixed with the sample prior to contacting with the solid phase and one would have been motivated to admix the detection antibody with the sample prior to immersing the solid phase multi-analyte card as combined to reduce the number of incubation steps and provide the advantage of reduction of assay time. One would have reasonably expected the modification to

be successful because Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988) teach that the all the assay reagents could be present simultaneously.

10. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990) and Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) as applied to claims 1, 2, 3, and 10 above, and further in view of Curtiss et al (U.S. Patent 4,677,057, published June 30, 1987).

Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990) and Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) are set forth supra. The combination differs by not assaying for other apolipoproteins (Apo AII), lipoproteins containing the apolipoproteins and determining the ratio of these.

Curtiss et al (U.S. Patent 4,677,057, published June 30, 1987) teach a solid phase immunoassays for Apo I and Apo AII using a monoclonal antibodies bound to a solid phase (see column 16, lines 36-68). Curtiss et al teach that the determination of APO AI and Apo AII are potentially useful to determine the prognosis of atherosclerosis or coronary artery disease (see column 5, lines 36-40).

It would have been *prima facie* obvious to one having ordinary skill in the art to substitute the solid phase immunoassay for Apo AII of Curtiss et al for the Apo AI assay in the multi-analyte method as combined supra because Curtis et al teach Apo AII was also an apolipoprotein marker

for HDL and that the levels of Apo AI and Apo AII were potentially useful in the prognosis of atherosclerosis or coronary artery disease.

11. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990) and Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) as applied to claims 1, 2, 3, and 10 above, and further in view of Koren et al (Atherosclerosis, 95:157-170, 1992).

Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990) and Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) are set forth supra. The combination differs by not assaying for other apolipoproteins (Apo E and Apo CIII), lipoproteins containing the apolipoproteins and determining the ratio of these.

Koren et al (Atherosclerosis, 95:157-170, 1992) teach monoclonal antibodies for Apo E and Apo CIII apolipoproteins (see pages 162-163) and their use in immunoassays.

It would have been *prima facie* obvious to one having ordinary skill in the art to substitute the monoclonal antibodies of Koren et al to assay for the apolipoprotein E or C III for either the Apo AI or Apo B100 in the multi-analyte method as combined *supra* because Koren et al monoclonal antibodies which bind ApoE and Apo CIII could be used in a solid phase immunoassay and the substitution of one analyte for another is routine in the art. One would have been motivated to substitute the other apolipoproteins in the method as combined in order to study their role, if any, in coronary artery disease or atherosclerosis.

12. Claims 1, 2, 3, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990) and Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) as applied to claims 1, 2, 3, and 10 above, and further in view of Luca (EP 0 407 035, published 2/3/88.

Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990) and Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) are set forth supra. The combination differs by not assaying for the presence of lipid associated with lipoproteins or apolipoproteins using as the detection means a lipid stain.

Luca teaches a method for the determination of lipid and/or apoprotein moiety of intact lipoproteins. Luca teaches capturing lipoproteins in a biological sample with an antibody (i.e. polyclonal, monoclonal claims 1-2; page 19) immobilized on a solid support which binds and epitope on an apolipoprotein and staining at least one fraction of the lipid contained in the lipid moiety of the captured lipoprotein by means of a lipid probe which becomes incorporated into the lipid moiety of the captured lipoprotein, detecting the measured signal form the incorporated or attached lipid probe and relating the signal identity to the amount of the fractions of the lipid moiety. Luca teach that the determination of lipoproteins and lipids are important in the examination of coronary heart disease.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the multi-analyte solid phase card assay as combined supra by replacing the detection antibody with the lipid probe of Luca et al because Luca teach that lipid

probes as a means for the determination and quantitation of lipid associated with an apolipoprotein in an intact lipoprotein as a means to study coronary heart disease and Fish et al teach that probes which provide for a color change are sufficient for analyte detection.

13. Claims 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990) and Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990), Luca (EP 0 407 035, published 2/3/88) as applied to claim 10 above, and further in view of Mills et al (Laboratory Techniques in biochemistry and molecular biology, Volume 14, A Guidebook to Lipoprotein Technique; 1984, pages 472-478).

Fish et al (U.S. Patent No. 5,126,276, published June 30, 1992), Scripps Clinic and Research Foundation (EP 0 262 854, published April 6, 1988), Forster et al (Biochem. Soc. Trans. 18(6):1180, December 1990) and Zhow et al (Hubi Yixueyuan Xueabo., Vol II, No.4, pp. 298-302, 1990) and Luca (EP 0 407 035, published 2/3/88) are set forth supra. The combination differs by not assaying for the presence of lipid associated with lipoproteins or apolipoproteins using as the detection means a the lipid stains the lipid stains Oil Red O and Sudan Black B.

Mills et al teach conventional and routine methods of staining lipids using routine and conventional stains such as Oil Red O and Sudan Black B (page 473-475). Mills et al also teach that Sudan Black can be used to pre-stain lipoproteins in plasma.

As to claim 7, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute Oil Red O or Sudan Black B for the lipid stain in the method as *supra* for claim 10 because Mills et al teach that lipids are conventionally detected using the Oil Red O and Sudan Black B. As to claim 8, it would have been *prima facie* obvious

to one of ordinary skill in the at the time the invention was made to pre-stain the sample lipoproteins in the method as opposed to subsequent staining of the lipoproteins using the prestaining method with Sudan Black B as taught by Mills et al because Mills et al teach that the lipoproteins in a plasma sample can be detected even if they are prestained.

14. Claims 42-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koren et al (Atherosclerosis, 95:157-170, 1992).

Koren et al teach a panB monoclonal antibody (see page 162, column 1, first full paragraph) and a monoclonal antibodies which bind Apo CIII (page 162, column 2, lines 14-19) and two monoclonal antibodies for ApoE, one which predominately binds HDL and LDL and the other which shows a higher affinity for VLDL (see page 162, column 2, lines 19-24). Koren et al also teaches polyclonal antibodies for Apo AI. Koren et al teach that these antibodies are useful in the study of the clinical significance of specific lipoprotein subspecies as atherogenic or antiatherogenic in response to the effect of a lipid lowering treatment. Koren et al differ by not having a monoclonal antibody which binds Apo AI and not assembling the antibodies into a kit format.

Curtiss et al (U.S. Patent 4,677,057, published June 30, 1987) teaches monoclonal antibodies specific for apolipoprotein AI (ApoAI) and apolipoprotein AII (ApoAII; see column 22, lines 34-67). Curtiss et al teach that the monoclonal antibody HA61 H112F3.1A11 (HB 8743) bound 100 percent of ApoA II on HDL and that all ApoII molecules expressed the epitope defined by this antibody (see column 27, fifth full paragraph to column 28, first full paragraph). This antibody meets the limitation of stable conformational epitope uninfluenced by other lipoproteins (i.e. specific binding). Curtiss et al teach diagnostic systems (i.e. kit) combining two or more such receptors (see column 22, seventh full paragraph). Curtiss et al teach that the

determination of APO AI and Apo AII are potentially useful to determine the prognosis of atherosclerosis or coronary artery disease (see column 5, lines 36-40).

It would have been *prima facie* obvious to one having ordinary skill in the art to substitute the assay of Curtiss using the monoclonal Apo A-I and Apo A-II antibodies in the assay of Koren et al because Curtiss et al teach that the monoclonal antibodies are useful to detect Apo AI and Apo AII levels and these levels are potentially useful to determine the prognosis of atherosclerosis or coronary artery disease (see column 5, lines 36-40). It also would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to assemble all the assay reagents in a kit format in order to perform the methods as combined because one would have been motivated to study the effect of other lipid lowering treatments on the levels of atherogenic or antiatherogenic lipoprotein subspecies.

Status of Claims

15. Claims 1-13 and 39-47 are rejected.

Conclusion

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on

the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

17. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy, Ph.D. whose telephone number is (703) 305-7555. The examiner can normally be reached on Monday-Friday from 6:30 AM to 3:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995.

Patricia A. Duffy, Ph.D.
June 20, 2000

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Primary Examiner
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